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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,569	NORRBY, KLAS	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-40 and 42-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-40 and 42-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20071001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Information Disclosure Statement (IDS) filed 1 October 2007 has been entered. Applicant's amendments of the specification and the claims filed on 3 December 2007 have been entered.

Claims 1-32 and 41 have been cancelled. Claim 53 is added. Claims 33-40 and 42-53 are pending and under examination.

Specification

The objection to the Abstract for using legal phraseology is withdrawn in response to Applicant's amendment of the claims.

Claim Objections/Rejections Withdrawn

The objection to claims 33, 40 for informalities is withdrawn in response to Applicant's amendment of the claims.

The objection to claim 40 for using improper Markush group language is withdrawn in response to Applicant's amendment of the claims.

The rejections of claims 33, 34, 40, 42, 46, 47 and 49-52 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention, is withdrawn in response to Applicant's amendment of the claims. These rejections include: claims 33 and 40 for reciting "states of tissue hypoperfusion with hypoxic or ischemic

consequences"; claims 34 and 47 for reciting the phrase "such as"; claims 34 and 47 for reciting "peripheral artery occlusive disease with or without impending gangrene"; claims 40 and 49-52 for lack of antecedent basis for the limitation of "the selected substance" or "said substance"; claim 42 for reciting "the peptide comprises a peptide formed of the sequences constituted of amino acids 16-40 and amino acids 18-40 from the N-terminal end of human lactoferrin"; and claim 46 for the recitation "based on the sequence".

The rejection of claims 33-38 and 40-51 under 35 U.S.C. 102(b) as being anticipated by Mamoru et al. (JP 07-278011), is withdrawn in response to Applicant's amendment of the claims to limit that the method does not pertain to coronary ischemia.

The rejection of claims 33-52 under 35 U.S.C. 102(b) as being anticipated by Wu et al. (U. S. Patent No: 5,712,247), is withdrawn in response to Applicant's amendment of the claims to limit the vascular disease to be a non-coronary hypoxia or ischemia.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The amended claims 40, 42-44 and 47-52 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, for reasons of record in the previous office action.

Applicant argues that the claims have been amended to define the peptides used in the treatment as a genus of peptides all containing an amino acid sequence of at least 7 amino acids in length selected from the amino acid sequence that is amino acids 12-40 of human lactoferrin counted from the N-terminal end or a similar peptide which is modified such that C-20 is replaced by A, Q-22 is replaced by K and N-26 is replaced by D. Applicant argues that the peptides are further defined functionally, as "active in stimulating VEGF-mediated angiogenesis". Applicant argues that the genus of peptides used in the claimed methods is described by structure and function and asserts that the full scope of the genus in the claims is adequately described in the disclosure.

Applicant's arguments have been fully considered but have not been found to be persuasive.

The amended claims still encompass a large genus of peptides that the specification fails to provide adequate written description: for example, "a peptide having an amino acid sequence constituted of amino acid residues 12-40 of human lactoferrin; or a smaller fragment thereof which is at least 7 amino acids long; and optionally wherein said peptide is modified such that C-20 is replaced by A, Q-22 is replaced by K, and N-26 is replaced by D; wherein said peptide is active in stimulating VEGF- mediated angiogenesis (claim 40)". The claim language encompasses fragments and variants of amino acid residues 12-40 of human lactoferrin, and the peptide sequences do not even need to be identical to that of the human lactoferrin sequence, for example, "wherein the peptide comprises a peptide essentially corresponding to residues 18-31 of human lactoferrin" (claim 43)". Applicant has

described human apo-lactoferrin, and its natural metabolite, lactoferricin, which is generated by pepsin-cleavage from human lactoferrin. Applicant describes that the peptides include those disclosed in the sequence listing of WO 00/01730. However, the peptides disclosed in the WO 00/01730 have different properties, and exhibit anti-inflammatory, anti-infectious and anti-tumoral activities (pp. 4, lines 22-28). WO 00/01730 does not teach any of the peptide in the sequence listing possesses an activity of stimulating VEGF- mediated angiogenesis. Applicant fails to describe the genus of peptides with the recited activity, i.e., stimulating VEGF- mediated angiogenesis. There is no teaching regarding the relationship of structure to function, such as what structural features are required such that the peptides exhibit the recited activity. In the absence of the guidance regarding the correlation of structure to function, simply listing a large number of variants and fragment, does not meet the written description requirement for the genus. Moreover, MPEP 2163 states: a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Therefore, only human apo-lactoferrin, its natural metabolite lactoferricin, and a peptide consisting of the amino acid sequence which begins at position 12, 16, or 18, and ends at position 40, or the amino acid sequence which begins at one of the amino acids in positions 12 and 15-21, and ends with the amino acid in position 31, and optionally wherein said peptide is modified such that C-20 is replaced by A, Q-22 is

replaced by K, and N-26 is replaced by D, but not the full scope of the claimed substance is adequately described in the disclosure.

The amended claims 40 and 42-52 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: *a method for treatment of a vascular disease or states of tissue hypoperfusion, wherein the vascular disease or states of tissue hypoperfusion leads to hypoxia or ischemia in a patient, comprising administering to the patient a therapeutically effective amount of human apo-lactoferrin or human lactoferricin,* does not reasonably provide enablement for the genus of human lactoferrin peptides, for reasons of record in the previous office action.

Applicant argues that the amended claims are restricted to a limited genus of peptides described structurally and functionally. Applicant argues that the claims are also restricted to a limited genus of vascular disease or states of tissue hypoperfusion leading to hypoxia or ischemia in a patient, with the proviso that the method does not pertain to coronary ischemia.

Applicant's arguments have been fully considered but have not been found to be persuasive.

As set forth *supra* and in the previous office action, the claims still encompass and require the use of a genus of human lactoferrin peptides having all lengths, segments, and variations for treating a vascular disease or states of tissue hypoperfusion that leads to hypoxia or ischemia in a patient, for example, an impending

or manifested stroke, and a peripheral artery occlusive disease. The claims require that the peptides can stimulate VEGF- mediated angiogenesis. The specification discloses that human apo-lactoferrin and its natural metabolite lactoferricin can stimulate $VEGF_{165}$ induced angiogenesis, and has a pro-angiogenic effect *in vivo*. The specification, however, does not provide sufficient support for the genus of peptides. In fact, the specification has not shown any of these peptides that act in the same mode as human lactoferrin. While the prior art teaches peptides derived from human lactoferrin, such as in WO 00/01730, however, these peptides have different properties. Also, Hiroki et al. (JP 09-194388) teaches peptides that can be used for treating atherosclerosis, however, Hiroki et al. does not teach the instantly claimed genus that can exhibit the same therapeutic effect. As cited previously, the recited peptides can have the same amino acid sequences as fragments generated from bovine apo-lactoferrin, which, on the contrary to human apo-lactoferrin, significantly inhibits $VEGF_{165}$ induced angiogenesis (Nobby et al., reference provided in the previous office action). Therefore, in the absence of detailed guidance regarding the structure/function correlation, it would require undue experimentation for one of skill in the art to practice the scope of the invention as broadly claimed.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33 and 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 recites "the method comprising the following steps". However, there is only one step in the claim, i.e., administration step.

Claims 36-39 recite "said substance". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 33-40, 42-44 and 47-52 rejected under 35 U.S.C. 102(e) as being anticipated by Miller et al. (U. S. Patent No: 6,426,362 B1, which has a priority filing date of 8 October 1999).

The instant claims are drawn to a method of treatment of a vascular disease or states of tissue hypoperfusion, wherein said disease or states of tissue hypoperfusion leads to hypoxia or ischemia in a patient, with the proviso that said method does not pertain to coronary ischemia, the method comprising administering to the patient a therapeutically effective amount of: 1) human apo-lactoferrin; 2) human lactoferricin; or

3) a peptide having an amino acid sequence constituted of amino acids 12-40 of human lactoferrin, or a smaller fragment thereof which is at least 7 amino acids long, and optionally wherein e peptide is modified with C20A, Q22K and N26D; and wherein the peptide is active in stimulating VEGF-mediated angiogenesis (claim 33, 35, 40, 42-44, 48); wherein the method is used for treating stroke and a peripheral artery occlusive disease (claims 34, 47); wherein administration is orally, parenterally, locally or by inhalation (claims 36-38, 39, 49-51, 52).

The '362 patent teaches the use of a composition for ameliorating disruption of energy metabolism secondary to stress, wherein the composition comprises tocopherol and lactoferrin (see abstract). The '362 patent teaches that the stress condition includes hypoxia (column 12, lines 5-27). The '362 patent teaches that the composition can be useful for treatment of ischemic disorders such as stroke and heart attack (column 42, lines 27-36). The '362 patent teaches that the lactoferrin includes human lactoferrin, fragmentary derivatives, and ion-associated or lack thereof form (apo-lactoferrin) (column 15, lines 18-41; column 16, lines 13-47; column 10, lines 52-60). The '362 patent teaches different routes of administration, for example, oral, topical, parenteral, and intranasal administration (column 27, lines 21-25). Therefore, the '362 patent anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-40, 42-44 and 47-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hiroki et al. (JP 09-194388, Publication Date: 29 July 1997), in view of Clement (Acta Chir. Belg., 2000, 100(5):190-193).

The instant claims are drawn to a method of treatment of a vascular disease or states of tissue hypoperfusion, wherein said disease or states of tissue hypoperfusion leads to hypoxia or ischemia in a patient, with the proviso that said method does not pertain to coronary ischemia, the method comprising administering to the patient a therapeutically effective amount of: 1) human apo-lactoferrin; 2) human lactoferricin; or 3) a peptide having an amino acid sequence constituted of amino acids 12-40 of human lactoferrin, or a smaller fragment thereof which is at least 7 amino acids long, and optionally wherein e peptide is modified with C20A, Q22K and N26D; and wherein the peptide is active in stimulating VEGF-mediated angiogenesis (claim 33, 35, 40, 42-44, 48); wherein the method is used for treating stroke and a peripheral artery occlusive disease (claims 34, 47); wherein administration is orally, parenterally, locally or by inhalation (claims 36-38, 39, 49-51, 52); wherein the method is used as an alternative to conventional treatment of peripheral artery occlusive disease (claim 53).

Hiroki et al. teach treating vascular diseases, such as atheromatous atherosclerosis [0001] by using lactoferrins or a peptide derived from hydrolysis of human lactoferrin (see Abstract). Hiroki et al. teach that the lactoferrin can be isolated from human milk and is iron-unsaturated (apo-lactoferrin) [0012]. Hiroki et al. teach the

sequence of various peptides that can be used as the therapeutic agent. Hiroki et al. teach different forms of the therapeutic agent for administration, e.g., tablet, capsule, injection, ointment, aerosol, etc. [0016].

Hiroki et al., however, do not teach treating a vascular disease or states of tissue hypoperfusion which leads to hypoxia or ischemia in a patient, and such a disease or states of tissue hypoperfusion includes an impending or manifested stroke, and a peripheral artery occlusive disease.

Clement teaches that peripheral artery occlusive disease (PAOD) is a manifestation of atherosclerosis. Clement teaches that in PAOD patients, atherosclerotic narrowing is likely to be present in other territories such as the coronary and cerebral arteries; mortality and morbidity in PAOD will largely depend on impairment of the circulation in these areas more than on the local ischemia in the limbs. Clement teaches treatment with therapeutic angiogenesis for these patients (see Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hiroki et al., with those of Clement to use human apo-lactoferrin for the treatment of PAOD. One of ordinary skill in the art would have been motivated to do so, because Hiroki et al., teach that human apo-lactoferrin, or a hydrolyzed peptide thereof, is useful for treating atherosclerosis, and Clement teaches that peripheral artery occlusive disease (PAOD) is a manifestation of atherosclerosis. Therefore, the combined teachings provide a reasonable expectation of successfully treating PAOD in a patient.

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-

273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
February 3, 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646